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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,715	03/04/2005	Stefan Golz	Le A 35 949	3124

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Barbara A. Shimci
Director, Patents & Licensing
Bayer HealthCare LLC - Pharmaceuticals
555 White Plains Road, Third Floor
Tarrytown, NY 10591

EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,715	GOLZ ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

This Office Action is in response to Applicants' amendment and remarks of 25 May 2008.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 May 2008 has been entered.

Applicants' response, received on 25 May 2008, has been entered. Claims 1-11 are pending in the instant application. Claims 1-3 have been amended and the amendments made of record. Claims 1-11 are currently under consideration.

Maintained Rejections

35 U.S.C. § 112, First Paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 1-11 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record and reasons set forth below.

Applicants traverse the rejection (Remarks of 25 May 2008, page 4, 3rd paragraph-page 5, 1st paragraph). The reasons for the traversal are:

At the priority date of this invention, the skilled artisan knew that stimulation of FPRL1 leads to an increase in intracellular Ca^{+2} concentration, as taught by Hu et al

(2001. J. Leukocyte Biology 70:155-61, cited by Applicants). Applicants assert that an increase of intracellular Ca^{+2} concentration in cardiomyocytes would trigger contraction, which directly relates to cardiac function. The specification discloses that FPRL1 mRNA is highly expressed in heart atrium and ventricle (Table I). Therefore, the skilled artisan can readily use the claimed screening methods to screen for therapeutic agents which regulate FPRL1 activity and could therefore treat heart failure. Identified inhibitors can be used to treat high-output heart failure and identified activators can be used to treat low-output heart failure.

Applicants' arguments have been fully considered but are not found to be persuasive for reasons of record and for reasons set forth below.

There is no dispute that the skilled artisan can perform the method steps recited in the claims of the instant invention; the issue at hand is whether an agonist or antagonist identified by the claimed method would be effective as a therapeutic agent to treat heart failure.

Hu et al teach that human phagocytic leukocytes express the GPCR FPRL-1; stimulation of the receptor in said cells increases intracellular calcium mobilization. Applicants assert that in cardiomyocytes, an increase of intracellular calcium ions following activation of FPRL1 would stimulate contraction of the cardiac cells.

However, the teachings of Hu et al. does not establish the required nexus between the FPRL1 polypeptide comprising the amino acid sequence of SEQ ID NO:2 and heart disease or heart failure. Neither the prior art nor the instant disclosure establishes that FPRL1 polypeptide modulates myocardial contractility or that an altered activity of the FPRL1 polypeptide leads to heart failure. Furthermore, in order to screen for a therapeutic agent that is useful in the treatment of heart failure, a causative link between the FPRL1 polypeptide and a specific type of heart failure is required. Without such knowledge, one of skill in the art would have to undertake undue experimentation to determine what type of therapeutic compound, an agonist or antagonist of FPRL1, is useful in treating heart failure.

As previously discussed, Table 1, a table of relative expression of FPRL1 in various human tissues confirms teachings in the art, that FPRL1 is expressed in a wide variety of tissues. It is noted that FPRL1 mRNA expression is higher in leukocytes, esophagus, bone marrow, placenta, spleen, liver, brain tissue, and breast and lung tumor than it is in any cardiovascular tissue. It is also noted that in the whole heart, the relative expression of FPRL1 is comparatively low (241 vs 13216 in the esophagus). One of ordinary skill in the art would not detect a pattern of unique expression of FPRL1 RNA in any one specific tissue or organ system, much less in the cardiovascular system. The evidence presented here constitutes an invitation to further experimentation to determine the role of FPRL1 in diseases of the heart.

Thus, given that the FPRL1 polypeptide is ubiquitously expressed, and does not show a predominant expression in heart or in cardiovascular tissue, and is not known to be associated with heart failure, one of ordinary skill in the art would be unable to predict that an agent identified by the methods of the instant invention would be effective in the treatment of heart failure. Clearly, further research would be required to determine whether there is a causative link between the FPRL1 polypeptide and a specific heart failure and whether an agonist or an antagonist of the FPRL1 screened by the instantly claimed method can be used to treat heart failure. Such research would constitute undue experimentation.

Therefore, the rejection is maintained.

35 U.S.C. § 102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claims 1, 2, 4, 5 and 10 under 35 U.S.C. § 102(b) as being anticipated by Gronert et al (1998, J Exp Med. 187:1285-1294) is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Remarks of 25 May 2008, page 5, 2nd and 3rd paragraphs). The reasons for the traversal are that each of independent claims 1 and 2 recites a step which refers to heart failure, which Gronert does not disclose.

Applicants' arguments have been fully considered but are not found to be persuasive for reasons of record and for reasons set forth below.

The claims are directed to a screening method. The recitation of "screening for therapeutic agents useful in the treatment of heart failure", has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a method, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Furthermore a recitation of "useful in the treatment of heart failure" in section iii of Claim 1 and section ii of Claim 2 do not recite steps to be performed in the practice of the methods of the instant invention.

The method steps comprise:

Claim 1:

i) contacting test compound with an FPRL1 polypeptide comprising the amino acid sequence of SEQ ID NO:2

ii) detecting binding of said test compound to said FPRL1 polypeptide

Claim 2:

i) determining the activity of an FPRL1 polypeptide comprising the amino acid sequence of SEQ ID NO:2 in the presence and absence of a test compound

ii) identifying the test compound as a potential therapeutic agent if the activity of the FPRL1 polypeptide is regulated in the presence but not the absence of the test compound.

As previously discussed, Gronert et al. teach cloning of the human enterocyte LXA4 receptor protein (identified as FPRL1 in the instant invention, accessible in public databases as NM_001462) which is 100% identical to SEQ ID NO:2 of the instant invention. Gronert et al. teaches contacting monolayers of T84 cells, which express the LXA4 receptor (identical to FPRL1), with LXA4 (test compound) and measuring inhibition of TNF-α- induced IL-8 release from the cells (a biological response indicating regulation of the FPRL1 receptor activity). The cells are grown as a monolayer; therefore the polypeptide is attached to a solid support. One of ordinary skill in the art would recognize that stimulating a biological activity of the LXA4 receptor by a test compound, would require binding of said test compound to the cognate receptor and is thus an inherent component of the method taught by Gronert et al.

Gronert et al does not refer to heart failure.

In response to applicant's argument that Gronert et al does not refer to heart failure:

As set forth in the rejection under 35 USC §112, 1st paragraph, no connection between FPRL1 expression or activity or changes in expression or activity and heart failure has been established nor would such a nexus be predictable. As previously discussed, neither the prior art nor the instant disclosure establishes that FPRL1 polypeptide modulates myocardial contractility or that an altered activity of the FPRL1 polypeptide leads to heart failure and thus an enabling disclosure has not been provided.

Furthermore, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

References to treatment of heart failure do not constitute method step, as the claims are not directed to a method of treatment but rather to a screening method. Therefore, only the actual method steps are considered in formulating the rejection and the teachings of Gronert et al anticipate the limitations of claims 1, 2, 4, 5 and 10.

The rejection is therefore maintained.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claims 3, 6, 8, and 9 under 35 U.S.C. 103(a) as being unpatentable over Gronert et al as applied to claim 1 in view of Fiore et al (1994, J Exp Med. 180:253-260) is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Remarks of 25 May 2008, pages 6 and 7). The reason for the traversal is that there is no *prima facie* case of obviousness because Gronert et al do not disclose a connection between the recited polypeptide and heart failure which is recited in each of independent claims 1 and 2. Fiore et al does not remedy this deficiency as it does not disclose expression of FPRL1 in the heart at all, much less specifically in the ventricle or atrium.

Applicant's arguments have been fully considered but are not found to be persuasive.

In response to applicant's argument that Gronert et al does not refer to heart failure: As set forth in the rejection under 35 USC §112, 1st paragraph, no connection between FPRL1 expression or activity or changes in expression or activity and heart failure has been established nor would such a nexus be predictable. As previously

discussed, neither the prior art nor the instant disclosure establishes that FPRL1 polypeptide modulates myocardial contractility or that an altered activity of the FPRL1 polypeptide leads to heart failure and thus an enabling disclosure has not been provided.

Furthermore, as discussed above, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

The recitation of treatment of heart failure do not constitute method step, as the claims are not directed to a method of treatment but rather to a screening method. As previously discussed, neither the prior art nor the instant disclosure establishes that FPRL1 polypeptide modulates myocardial contractility or that an altered activity of the FPRL1 polypeptide leads to heart failure and thus an enabling disclosure has not been provided.

Therefore, only the actual method steps are considered in formulating the rejection.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As previously indicated:

Fiore et al. teach identification of a high affinity LXA4 receptor protein (identified as FPRL1 polypeptide in the instant invention). The reference teaches expression of the receptor in Chinese hamster ovary cells (CHO) and measurement of the binding of [^{3}H]LXA4 (labeled ligand or test compound, compound known to be a regulator of the receptor) to intact cell suspensions and subcellular fractions. The reference teaches eicosanoid competition of [^{3}H]LXA4 binding, utilizing different concentrations of test eicosanoid compounds.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Gronert et al and utilize labeled [^{3}H]LXA4 (labeled ligand or test compound) to assay binding to intact cell suspensions and subcellular fractions and to measure eicosanoid competition of [^{3}H]LXA4 binding. The person of ordinary skill in the art would have been motivated to make that modification and anticipate success because both references teach assays using the FPRL1 receptor, also known as the LXA4 receptor.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., expression of FPRL1 in the heart at all, much less specifically in the ventricle or atrium I) are not recited in the rejected claim(s). The independent claims 1-3 recite contacting a test compound with a FPRL1 polypeptide comprising the amino acid sequence of SEQ ID NO:2, which is 100% identical to sequence taught by Gronert et al. The claims do not require that this sequence be expressed in heart tissue, nor do they recite any specific source of said sequence. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The rejection is therefore maintained.

The rejection of Claim 7 under 35 U.S.C. 103(a) as being unpatentable over Gronert as applied to claim 1 in view of Ramakrishnan (US PGPub 2002/0058259, filed 14 March 2001) is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Remarks of 25 May 2008, pages 6 and 7). The reason for the traversal is that there is no *prima facie* case of obviousness because Gronert et al do not disclose a connection between the recited polypeptide and heart failure which is recited in each of independent claims 1 and 2. Applicants argue that Ramakrishnan does not remedy this deficiency as Ramakrishnan discloses a GPCR related to FPRL1 which is not expressed in the heart.

Applicant's arguments have been fully considered but are not found to be persuasive.

As previously indicated:

Ramakrishnan teaches that in binding assays, either the test compound or the lipoxin A4 receptor-like polypeptide (an FPRL1 type receptor) can comprise a detectable label. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize the methods of Gronert et al and modify these methods to utilize a receptor polypeptide comprising a detectable label as taught by Ramakrishnan. The person of ordinary skill in the art would have been motivated to make that modification and anticipate success because Ramakrishnan teaches that in binding assays, either the test compound or the lipoxin A4 receptor-like polypeptide can comprise a detectable label.

In response to Applicants' traversal of Gronert reference: As set forth in the rejection under 35 USC §112, 1st paragraph, no connection between FPRL1 expression or activity or changes in expression or activity and heart failure has been established nor would such a nexus be predictable. As previously discussed, neither the prior art nor the instant disclosure establishes that FPRL1 polypeptide modulates myocardial contractility or that an altered activity of the FPRL1 polypeptide leads to heart failure and thus an enabling disclosure has not been provided.

In response to applicant's argument that Ramakrishnan discloses a GPCR related to FPRL1 which is not expressed in the heart:

Applicants are arguing limitations not recited in the claims. As noted above, the claims do not require that this sequence be expressed in heart tissue, nor do they recite any specific source of said sequence. Ramakrishnan is cited for its teachings that in binding assays the lipoxin A4 receptor-like polypeptide can be coupled to a detectable label, the limitation recited in Claim 7.

The rejection is therefore maintained.

The rejection of Claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Gronert et al as applied to claim 1 in view of Seo et al (1997, J Immunology 158:1895-1901) is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Remarks of 25 May 2008, pages 6 and 7). The reason for the traversal is that there is no *prima facie* case of obviousness because Gronert et al do not disclose a connection between the recited polypeptide and heart failure which is recited in each of independent claims 1 and 2. Applicants argue that Seo et al does not overcome the deficiency as Seo et al does not teach or suggest a connection between FPRL1 and heart failure.

Applicant's arguments have been fully considered but are not found to be persuasive.

As previously indicated:

The teachings of Gronert et al are reviewed in detail above. Gronert et al. do not teach a method wherein the compound is attached to a solid support.

Seo et al teach binding of a peptide (compound WKYMVm-NH2) immobilized on a biosensor chip to FPRL1 receptor expressed U266 cells.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize the methods of Gronert et al and modify these methods to utilize a test compound bound to a solid support as taught by Seo et al. The person of ordinary skill in the art would have been motivated to make that modification and expected success because both references teach binding of test compounds to the FPRL1 receptor and Suo et al teach assays utilizing test compounds immobilized on biosensor chips which bind to FPRL1 receptors on cells.

In response to Applicants' traversal of Gronert reference: As set forth in the rejection under 35 USC §112, 1st paragraph, no connection between FPRL1 expression or activity or changes in expression or activity and heart failure has been established nor would such a nexus be predictable. As previously discussed, neither the prior art nor the instant disclosure establishes that FPRL1 polypeptide modulates myocardial contractility or that an altered activity of the FPRL1 polypeptide leads to heart failure and thus an enabling disclosure has not been provided.

In response to Applicants argument that Seo et al does not teach or suggest a connection between FPRL1 and heart failure: the reference is cited to teach a binding

assay method wherein the test compound is attached to a solid support and binds to an FPRL1 receptor, the limitation recited in claim 11.

The rejection is therefore maintained.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/Ph.D.
Primary Examiner, Art Unit 1647

/Shulamith H. Shafer/ Ph.D.
Examiner, Art Unit 1647